The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours.

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Abstract: It has been 12 yr since the publication of the last World Health Organization (WHO) classification of tumours of the prostate and bladder. During this time, significant new knowledge has been generated about the pathology and genetics of these tumours. Intraductal carcinoma of the prostate is a newly recognized entity in the 2016 WHO classification. In most cases, it represents intraductal spread of aggressive prostatic carcinoma and should be separated from high-grade prostatic intraepithelial neoplasia. New acinar adenocarcinoma variants are microcystic adenocarcinoma and pleomorphic giant cell adenocarcinoma. Modifications to the Gleason grading system are incorporated into the 2016 WHO section on grading of prostate cancer, and it is recommended that the percentage of pattern 4 should be reported for Gleason score 7. The new WHO classification further recommends the recently developed prostate cancer grade grouping with five grade groups. For bladder cancer, the 2016 WHO classification continues to recommend the 1997 International Society of Urological Pathology grading classification. Newly described or better defined noninvasive urothelial lesions include urothelial dysplasia and urothelial proliferation of uncertain malignant potential, which is frequently identified in patients with a prior history of urothelial carcinoma. Invasive urothelial carcinoma with divergent differentiation refers to tumours with some percentage of "usual type" urothelial carcinoma combined with other morphologies. Pathologists should mention the percentage of divergent histologies in the pathology report. PATIENT SUMMARY Intraductal carcinoma of the prostate is a newly recognized entity in the 2016 World Health Organization classification. Better defined noninvasive urothelial lesions include urothelial dysplasia and urothelial proliferation of uncertain malignant potential.

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The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours

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Abstract

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Patient summary: Intraductal carcinoma of the prostate is a newly recognized entity in the 2016 World Health Organization classification. Better defined noninvasive urothelial lesions include urothelial dysplasia and urothelial proliferation of uncertain malignant potential.

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1. The new prostate tumour classification

The aim of this review is to summarize the new additions to the 2016 World Health Organization (WHO) classification (WHO "blue book") compared with the 2004 WHO classification, with emphasis on a new entity, new variants of acinar adenocarcinoma, and new imunohistochemical stains for diagnosis, grading, risk stratification, and molecular genetics of acinar adenocarcinoma of the prostate. The 2016 WHO classification of tumours of the prostate [1] is summarized in Figure 1.

1.1. New entity: intraductal carcinoma

Intraductal carcinoma is newly recognized as an entity in the 2016 WHO classification. This term has been used for several decades, dating back to at least 1985 [2], and it has been variably used to describe intraductal spread or in situ

WHO classification of tumours of the prostate

Epithelial tumours	
Glandular neoplasms	
Acinar adenocarcinoma	8140/3
Atrophic	
Pseudohyperplastic	
Microcystic	
Foamy gland	
Mucinous (colloid)	8480/3
Signet ring–like cell	8490/3
Pleomorphic giant cell	
Sarcomatoid	8572/3
Prostatic intraepithelial neoplasia, high-grade	8148/2
Intraductal carcinoma	8500/2
Ductal adenocarcinoma	8500/3
Cribriform	8201/3
Papillary	8260/3
Solid	8230/3
Urothelial carcinoma	8120/3
Squamous neoplasms	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Basal cell carcinoma	8147/3
Neuroendocrine tumours	
Adenocarcinoma with neuroendocrine differentiation	8574/3
Well-differentiated neuroendocrine tumour	8240/3
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mesenchymal tumours	
Stromal tumour of uncertain malignant potential	8935/1
Stromal sarcoma	8935/3
Leiomyosarcoma	8890/3
Rhabdomyosarcoma	8900/3
Leiomyoma	8890/0
Angiosarcoma	9120/3
Synovial sarcoma	9040/3
Inflammatory myofibroblastic tumour	8825/1
Osteosarcoma	9180/3
Undifferentiated pleomorphic sarcoma	8802/3
Solitary fibrous tumour	8815/1
Solitary fibrous tumour, malignant	8815/3
Haemangioma	9120/0
Granular cell tumour	9580/0
Haematolymphoid tumours	
Diffuse large B-cell lymphoma	9680/3
Chronic lymphocytic leukaemia / small lymphocytic lymphoma	9823/3
Follicular lymphoma	9690/3
Mantle cell lymphoma	9673/3
Acute myeloid leukaemia	9861/3
B lymphoblastic leukaemia/lymphoma	9811/3
Miscellaneous tumours	
Cystadenoma	8440/0
Nephroblastoma	8960/3
Rhabdoid tumour	8963/3
Germ cell tumours	
Clear cell adenocarcinoma	8310/3
Melanoma	8720/3
Paraganglioma	8693/1
Neuroblastoma	9500/3
Metastatic tumours	
Tumours of the seminal vesicles	
Epithelial tumours	
Adenocarcinoma	8140/3
Squamous cell carcinoma	8070/3
Mixed epithelial and stromal tumours	
Cystadenoma	8440/0
Mesenchymal tumours	
Leiomyoma	8890/0
Schwannoma	9560/0
Mammary-type myofibroblastoma	8825/0
Gastrointestinal stromal tumour, NOS	8936/1
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Liposarcoma	8850/3
Solitary fibrous tumour	8815/1
Haemangiopericytoma	9150/1
Miscellaneous tumours	
Choriocarcinoma	9100/3
Seminoma	9061/3
Well-differentiated neuroendocrine tumour / carcinoid tumour	8240/3
Lymphomas	
Ewing sarcoma	9364/3
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {917A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification {756A}, taking into account changes in our understanding of these lesions.

Fig. 1 – World Health Organization (WHO) classification of tumours of the prostate. Reproduced with permission from the WHO [1].
WHO = World Health Organization.

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growth of acinar or ductal adenocarcinoma of the prostate and intraductal proliferation of urothelial carcinoma [3–11]. The 2016 WHO definition is as follows: "Intraductal carcinoma of the prostate is intra-acinar and/or intraductal neoplastic epithelial proliferation that has some features of high-grade prostatic intraepithelial neoplasia (HGPIN) but exhibits much greater architectural and/or cytological atypia, typically associated with high-grade, high-stage prostate carcinoma."

Intraductal carcinoma is thought to represent a late event in prostate cancer evolution, with intraductal spread of aggressive prostatic carcinoma and cancerization of pre-existing ducts and acini by high-grade prostatic adenocarcinoma. A minority of cases, however, may be precursors to proliferation because in approximately 10% of radical prostatectomy (RP) cases following a needle biopsy diagnosis of intraductal carcinoma, the intraductal carcinoma in the whole prostate gland is found in pure form, without associated invasive adenocarcinoma [8].

Intraductal carcinoma is rare in isolated form in needle biopsy tissue, being detected in 0.1–0.3% of needle core cases [11,89], and is uncommon in the presence of invasive adenocarcinoma in needle core tissue, being diagnosed in 2.8% of such cases [11]. In whole prostate glands, the incidence is dependent on the grade and stage of the prostatic adenocarcinoma in the series and ranges from 20% to 40% of RP cases [5,10].

Diagnostic separation of intraductal carcinoma from HGPIN is critical due to the association of intraductal carcinoma with an average Gleason score of 8 and pT3 prostatic adenocarcinoma in the whole gland [8]. In contrast to HGPIN, intraductal carcinoma exhibits a solid or dense cribriform pattern or a loose cribriform or micropapillary pattern with either marked nuclear atypia (ie, nuclear size ≥6× normal) or comedonecrosis (Fig. 2) [11]. PTEN and ERG immunostaining may be a useful adjunctive method because intraductal carcinoma commonly shows PTEN loss and ERG expression, whereas PTEN loss is rare in HGPIN and ERG expression is uncommon [12].

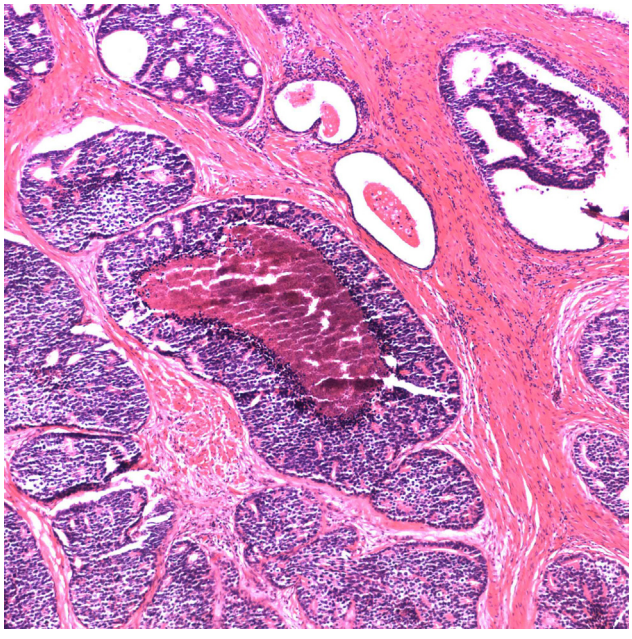

Fig. 2 – Intraductal carcinoma of the prostate with comedonecrosis, with surrounding dense cribriform glands.

An important point is that intraductal carcinoma is not assigned a Gleason grade [13].

Reporting of isolated intraductal carcinoma in needle biopsy should include a comment stating that intraductal carcinoma of the prostate is associated with high-grade and high-volume prostate carcinoma and that therapy may be indicated. Repeat biopsy may also be recommended.

1.2. New variants of acinar adenocarcinoma of the prostate

Variants of acinar adenocarcinoma of the prostate may be of significance due to difficulty in pathologic diagnosis and to prognostic and/or therapeutic differences compared with usual acinar adenocarcinoma [14]. The acinar adenocarcinoma variants that are difficult to diagnose look deceptively benign and are highlighted in the WHO classification. These include atrophic, pseudohyperplastic, foamy gland, and microcystic adenocarcinomas. Variants of acinar adenocarcinoma with worse prognosis compared with usual acinar adenocarcinoma include signet ring–like, sarcomatoid, and pleomorphic giant cell adenocarcinoma. The newly recognized acinar adenocarcinoma variants in the WHO 2016 classification are microcystic adenocarcinoma and pleomorphic giant cell adenocarcinoma [1].

Microcystic adenocarcinoma: Microcystic carcinoma is a deceptively benign-appearing variant of acinar adenocarcinoma of the prostate [15]. Cystic change in prostatic adenocarcinoma glands is unusual and may be confused with cystic change in benign glands, which is common. These dilated malignant microcystic glands are, on average, 10-fold larger than typical small gland adenocarcinoma of the prostate. Alpha-methylacyl-CoA racemase (AMACR) is expressed in almost all cases, and the glands uniformly lack basal cells in immunohistochemistry using p63 and 34βE12 antibodies. The Gleason grade is pattern 3.

Pleomorphic giant cell adenocarcinoma: Pleomorphic giant cell adenocarcinoma is a rare variant of acinar adenocarcinoma with giant, bizarre, anaplastic cells harbouring pleomorphic nuclei. Fewer than 10 cases have been reported [16,17]. Some patients have a history of hormonal or radiation therapy of usual acinar adenocarcinoma before the diagnosis of pleomorphic giant cell carcinoma is rendered. This variant is unusual in the degree of nuclear atypia because even the highest grade usual acinar adenocarcinomas typically display relatively uniform nuclei. The clinical course is typically highly aggressive.

1.3. New variant of neuroendocrine tumours of the prostate: large cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma of the prostate is a rare neuroendocrine tumour variant. It was not recognized in the 2004 WHO classification. The largest series, of seven cases, was published in 2006 [18]. Almost all cases arose after hormonal treatment of adenocarcinoma of the prostate. The

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histologic features are identical to large cell neuroendocrine carcinomas diagnosed in other anatomic sites such as the lung. Outcome is poor, with mean survival of 7 mo after platinum-based chemotherapy.

1.4. Immunophenotype

In 2004, the prostate tissue markers most commonly targeted in diagnostic immunohistochemistry included prostate-specific antigen (PSA), prostate-specific acid phosphatase (PAP), high-molecular-weight cytokeratins (using monoclonal antibody 34βE12), p63, and AMACR. These remain important immunostains in the diagnosis of selected cases of acinar adenocarcinoma of the prostate. In the 2016 WHO blue book, utilization of these immunostains and others is presented in specific differential diagnostic scenarios. New immunostains discussed include the prostatic markers prostein (also known as P501S, a plasma membrane protein) and NKX3.1 (a homeobox-containing transcription factor) [19–22]. Immunohistochemical detection of NKX3.1 can be particularly valuable for confirmation of a PSA- and/or PAP-negative prostatic carcinoma when urothelial carcinoma is in the differential diagnosis and for the diagnosis of metastatic adenocarcinoma of the prostate. PSA, PAP, prostein, and NKX3.1 immunostains are all highly sensitive for diagnosis of metastatic prostatic adenocarcinoma, with each displaying >94% sensitivity [19,21]. PSA and PAP expression can be decreased after androgen deprivation therapy, and prostein and NKX3.1 immunostains can be of use in such cases.

1.5. Grading of adenocarcinoma of the prostate

Gleason grading remains the standard approach to histologic grading of adenocarcinoma of the prostate. Since the 2004 WHO classification, there have been modifications to the Gleason grading system, and these were incorporated into the 2016 WHO section on grading of prostate cancer. In addition, for Gleason score 7 adenocarcinomas, reporting percentage of adenocarcinoma that is pattern grade 4 is recommended, and grade groups are introduced.

2014 International Society of Urological Pathology modifications of Gleason grading: Significant evidence-based modifications of Gleason grading are presented, based on an International Society of Urological Pathology (ISUP) meeting in 2014 [23]. The major conclusions, which are rendered in that publication [23] and in the 2016 WHO blue book [1], are as follows:

- Cribriform glands should be assigned Gleason pattern 4.
- Glomeruloid glands should be assigned Gleason pattern 4.
- Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern rather than grading them all as 4.

Some cases of cribriform adenocarcinoma have been graded as pattern 3 in the past, and according to the 2004 WHO blue book [24], rare cribriform glands could be diagnosed as pattern 3. Nevertheless, recent data from several institutions have clearly demonstrated that cribriform adenocarcinoma is independently associated with biochemical failure after RP [25,26], with metastasis after RP [27], and with metastasis-free and disease-specific survival [27]. All cribriform adenocarcinomas should be assigned pattern 4.

An additional change from the 2004 WHO classification is the addition of poorly formed glands to pattern 4. High-grade pattern 4 now comprises cribriform glands, fused glands, poorly formed glands, and glomeruloid glands.

A new modified Gleason grading diagram (Fig. 3) is presented in the ISUP publication [23] and in the 2016 WHO blue book [1]. This diagram is significantly different from the diagram published in the 2004 WHO blue book [24]. Cribriform glands are now pattern 4, and poorly formed glands are included as pattern 4 in the new diagram.

Reporting of adenocarcinoma that is pattern 4: It is recommended in the 2016 WHO blue book that percentage of pattern 4 be reported for Gleason score 7 when this is the highest grade in needle biopsy or RP cases. This is a change from the 2004 WHO blue book, which indicated that reporting of high-grade patterns 4 and 5 was not routine in clinical practice [24]. The percentage of pattern 4 may have

Fig. 3 – Modified Gleason grading schematic diagram, according to the International Society of Urological Pathology. Reproduced with permission from Indiana University.

implications for management strategies such as active surveillance (AS) because some patients with Gleason grade 3 + 4 = 7 with a low percentage of pattern 4 may be considered for AS [28]. An abundance of data suggests that percentage of adenocarcinoma that is high-grade pattern 4/5 is an important prognostic indicator [29–31]. The method for determination of percentage of pattern 4 was not specified.

Grade groups: A new set of grade groups was recently developed [13,32], with a broad consensus for acceptance by expert urologic pathologists and clinicians at the 2014 ISUP consensus conference on Gleason grading of prostatic carcinoma [23]. These grade groups are as follows:

- Grade group 1: Gleason score $\leq$6
- Grade group 2: Gleason score 3 + 4 = 7
- Grade group 3: Gleason score 4 + 3 = 7
- Grade group 4: Gleason score 4 + 4 = 8, 3 + 5 = 8, 5 + 3 = 8
- Grade group 5: Gleason scores 9–10

There are several rationales for the generation of the grade groups: Gleason scores 2–5 are rarely used, Gleason scores have been grouped together in the past in arrangements that do not accurately reflect prognosis, and grade group 1 signifies to the clinician and the patient that Gleason score 6 is the lowest possible grade rather than an intermediate grade 6 of 10. The latter point is critical and informs all concerned that a diagnosis of adenocarcinoma of the prostate, grade group 1, carries an excellent prognosis [13,32]. Many patients with grade group 1 tumours, in the correct clinical context with consideration of other parameters (eg, serum PSA level, clinical stage, and amount of cancer in needle core tissue), could be candidates for AS. The prognostic impact of the five grade groups has been validated in a large multi-institutional study of >20 000 RP cases, >16 000 needle biopsy cases, and >5000 biopsies followed by radiation therapy [13]. Of interest, there are genomic correlates and molecular support for the grade group system [33]. The 2016 WHO blue book states that the grade groups should be reported in conjunction with the 2014 modified ISUP Gleason scores.

1.6. Risk stratification and active surveillance for acinar adenocarcinoma of prostate

In the 2016 WHO blue book, the vital importance of risk stratification for patients with adenocarcinoma of the prostate is highlighted in a section on prognosis and predictive factors [1]. In particular, there is much detail on pathologic prognostic factors for the different types of tissue samples: needle biopsy, transurethral resection, and RP tissues. In addition, the 2015 National Comprehensive Cancer Network risk groups, which use clinical and pathologic factors, are presented in a table. Because many prostate cancers (especially many grade group 1 tumours) are indolent and may be managed by AS, a new discussion is provided on AS, along with a table on clinical and pathologic inclusion criteria used by a number of large AS programs.

1.7. Genetic profile of adenocarcinoma of the prostate

Since 2004, there has been a remarkable expansion of knowledge about the genetics of prostate cancer. Advances in sequencing technology have revealed complex rearrangements and marked heterogeneity [34–37]. Only a few abnormalities in specific genes are highly recurrent, but alterations in certain signalling pathways predominate, such as PI3K/PTEN/AKT, cell cycle regulation, and chromatin regulation [34]. The most common alterations, in both primary and metastatic prostate cancer, are fusions of androgen-regulated promoters with *ERG* and other members of the *ETS* family of transcription factors [37], particularly the *TMPRSS2-ERG* fusion, which is present in approximately 50% of all prostate cancers. In primary clinically localized prostate cancer, there are relatively few recurrent nonsynonymous point mutations, including mutations in the *SPOP* (11%) and *FOXA1* (3%) genes [37]. In comparison, in castration-resistant metastatic prostate cancer, there are increased alteration rates in many genes and pathways, including abnormalities in androgen receptor (AR) signalling (usually due to *AR* gene amplification or mutation), DNA repair, and PI3K pathways, as well as mutations or deletions in the *TP53*, *RB1*, *KMT2C*, and *KMT2D* genes [36,37]. This landscape of somatic genetic abnormalities in adenocarcinoma of the prostate is discussed in depth in a genetic profile section, and a model for molecular classification of prostate cancer is shown. Although this molecular classification is not currently in clinical use, the discovery of these genetic abnormalities has led to greater understanding of the molecular pathogenesis of prostate cancer and has demonstrated potentially therapeutically actionable molecular defects. Such molecular classifications may be incorporated into WHO classifications of prostate cancer in the future.

2. The new bladder tumour classification

The fourth edition of the WHO classification of tumours of the urothelial tract provides a contemporary review of the morphology of urothelial neoplasms, emphasizing their unique ability to exhibit divergent differentiation, multiple morphologic variants, and a diverse genomic landscape (Fig. 4) [1]. It is becoming clearer how both morphology and genotype may be exploited to select therapy, and for the latter, clinical protocols are in place to take advantage of activated molecular pathways in specific tumours. What follows is not a comprehensive summary of the entire WHO narrative but rather a selected summary of new or evolving concepts or entities. Mesenchymal, neuroendocrine, and other types of nonurothelial lesions are beyond the scope of this summary.

2.1. Grading of urothelial tumours

Grading of urothelial tumours has particular importance in noninvasive disease, specifically papillary neoplasms. Although a small percentage of invasive carcinomas are low grade, usually limited to the lamina propria, >95% of

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WHO classification of tumours of the urothelial tract

Urothelial tumours	
Infiltrating urothelial carcinoma	8120/3
Nested, including large nested	
Microcystic	
Micropapillary	8131/3
Lymphoepithelioma-like	8082/3
Plasmacytoid / signet ring cell / diffuse	
Sarcomatoid	8122/3
Giant cell	8031/3
Poorly differentiated	8020/3
Lipid-rich	
Clear cell	
Non-invasive urothelial neoplasms	
Urothelial carcinoma in situ	8120/2
Non-invasive papillary urothelial carcinoma, low-grade	8130/2
Non-invasive papillary urothelial carcinoma, high-grade	8130/2
Papillary urothelial neoplasm of low malignant potential	8130/1
Urothelial papilloma	8120/0
Inverted urothelial papilloma	8121/0
Urothelial proliferation of uncertain malignant potential	
Urothelial dysplasia	
Squamous cell neoplasms	
Pure squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Squamous cell papilloma	8052/0
Glandular neoplasms	
Adenocarcinoma, NOS	8140/3
Enteric	8144/3
Mucinous	8480/3
Mixed	8140/3
Villous adenoma	8261/0
Urachal carcinoma	8010/3
Tumours of Müllerian type	
Clear cell carcinoma	8310/3
Endometrioid carcinoma	8380/3
Neuroendocrine tumours	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Well-differentiated neuroendocrine tumour	8240/3
Paraganglioma	8693/1
Melanocytic tumours	
Malignant melanoma	8720/3
Naevus	8720/0
Melanosis	
Mesenchymal tumours	
Rhabdomyosarcoma	8900/3
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Inflammatory myofibroblastic tumour	8825/1
Perivascular epithelioid cell tumour	
Benign	8714/0
Malignant	8714/3
Solitary fibrous tumour	8815/1
Leiomyoma	8890/0
Haemangioma	9120/0
Granular cell tumour	9580/0
Neurofibroma	9540/0
Urothelial tract haematopoietic and lymphoid tumours	
Miscellaneous tumours	
Carcinoma of Skene, Cowper, and Littre glands	8140/3
Metastatic tumours and tumours extending from other organs	
Epithelial tumours of the upper urinary tract	
Tumours arising in a bladder diverticulum	
Urothelial tumours of the urethra	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (917A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification (756A), taking into account changes in our understanding of these lesions.

Fig. 4 – World Health Organization (WHO) classification of tumours of the urothelial tract. Reproduced with permission from the WHO [1]. WHO = World Health Organization.

invasive tumours are high grade. Exceptions exist, a good example being the nested variant of urothelial carcinoma, which, despite its deceptively bland cytomorphology, may present as locally advanced disease and is associated with poor outcome. Noninvasive tumours can be divided into two categories: papillary or flat. Carcinoma devoid of papillary structures is called *carcinoma in situ* (CIS) and is, by definition, high grade. Importantly, flat urothelium can exhibit a wide spectrum of atypia, from reactive to preneoplastic to frankly malignant. Papillary tumours are also quite varied, including reactive proliferations and papilloma as well as papillary urothelial proliferation of low malignant potential (PUNLMP) and low- and high-grade papillary carcinoma [38]. Interobserver variability is high, even among experienced pathologists, despite many decades of efforts to develop pathologic classifications that best reflect clinical behaviour [39–50]. As in 2004, the 2016 WHO classification continues to recommend the application of the grading classification first put forth by ISUP in 1997 (Table 1). In fact, this classification continues to be endorsed by ISUP and all major contemporary pathology textbooks and guidelines, including the *AFIP* [US Armed Forces Institute of Pathology] *Atlas of Tumor Pathology, Series 4* fascicle on tumours of the kidney, bladder, and related urinary structures and the latest editions of the American Joint Committee on Cancer *Cancer Staging Manual* and the International Collaboration on Cancer Reporting. Multiple studies have been published comparing this classification with others, particularly the 1973 WHO classification, in terms of reproducibility and

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Table 1 – World Health Organization classification of tumours: tumours of the urothelial tract, differences between the third and fourth editions for noninvasive urothelial lesions

Third edition [51]:	Fourth edition [1]:
Noninvasive urothelial lesions	*Noninvasive urothelial lesions*
Urothelial carcinoma in situ	Urothelial carcinoma in situ
Papillary urothelial carcinoma, low grade	Papillary urothelial carcinoma, low grade
Papillary urothelial carcinoma, high grade	Papillary urothelial carcinoma, high grade
Papillary urothelial neoplasm of low malignant potential	Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma	Urothelial papilloma
Inverted urothelial papilloma	Inverted urothelial papilloma
	Urothelial proliferation of uncertain malignant potential (hyperplasia)
	Urothelial dysplasia

clinical impact. Results have been mixed but mostly positive. It is recommended that this classification be adopted worldwide because of its inherent advantages:

- Uniform terminology and definitions based on the level of cytologic and architectural abnormalities (order and disorder) and the establishment of detailed criteria for various preneoplastic conditions and tumour grades
- Definition of a group of lesions (high grade) with a high risk of progression that may be candidates for adjuvant therapy
- Elimination of ambiguity in diagnostic categories in the 1973 WHO system (grade 1–2, grade 2–3)
- Inclusion of a category of papillary neoplasm (ie, PUNLMP) that is not associated with invasion at the time of diagnosis and has a negligible risk of progression, although the potential for recurrence requires clinical surveillance

Admittedly, controversy remains, and the reasons are multifactorial but mainly due to the fact that the clinical risk of recurrence and progression are determined not solely by growth pattern and grade but also by other factors such as size, multifocality, time to recurrence, and prior intravesical therapy. In addition, we must accept the fact that grading is largely subjective and that, in the future, ancillary studies (either immunohistochemical or molecular assays) will lead to enhanced reproducibility and better correlation with clinical outcome [52].

The term *urothelial proliferation of uncertain malignant potential* has been introduced, supplanting the term *hyperplasia* [53–58]. It describes a thickened urothelium with minimal or no cytological atypia and no true papillary fronds, although undulations are common. These entities may be seen de novo, and in this setting, the clinical relevance is unknown. More frequently they are seen in patients who have a history of prior carcinoma or seen adjacent to papillary lesions. It is likely that most represent lateral extension ("shoulder lesion") of a papillary neoplasm; this assumption is supported by high incidence of chromosome 9 deletions and lesser but significant incidence of *FGFR3* abnormalities.

Urothelial dysplasia is defined as a flat lesion with appreciable cytologic and architectural abnormalities that are believed to be preneoplastic but that fall short of the criteria required for urothelial CIS. It is rarely described de novo, and for this reason, it is poorly studied. More important, it is the most difficult category to define morphologically because of significant interobserver variability and the total absence of large clinical studies documenting its relationship to the development of subsequent CIS. In patients with a prior history of urothelial carcinoma, this diagnosis is particularly challenging and fraught with variability in interpretation, given the changes induced by prior instrumentation, biopsy site changes, and intravesical therapy. It is of no surprise that urologists rarely alter management based on this diagnosis alone.

2.2. *Invasive urothelial carcinoma with divergent differentiation*

By definition, urothelial carcinoma with divergent differentiation refers to tumours arising within the urothelial tract, in which some percentage of "usual type" urothelial carcinoma is present along with other morphologies (Fig. 5a, Table 2). Urothelial carcinoma has long been known to have a remarkable propensity for divergent differentiation, which is seen most commonly in association with high-grade and locally advanced disease [59–62]. The incidence of divergent differentiation in cystectomy specimens is as high as 33%. Its presence is associated with established predictors of aggressive behaviour, and although some studies have found an association with adverse outcome on univariate analysis, the effect does not remain significant on multivariable analysis. The amount of divergent histology present does not seem to have a bearing on outcome, although limited data are available to this effect [61]; however, it is recommended that pathologists report the percentage of divergent histologies in the pathology report.

Table 2 – World Health Organization classification of tumours: tumours of the urothelial tract, differences between the third and fourth editions, invasive urothelial tumors

Third edition [51]:	Fourth edition [1]:
Invasive urothelial tumours	*Invasive urothelial tumours*
Infiltrating urothelial carcinoma	Infiltrating urothelial carcinoma with divergent differentiation
with squamous differentiation	Nested, including large nested
with glandular differentiation	Microcystic
with trophoblastic differentiation	Micropapillary
Nested	Lymphoepithelioma-like
Microcystic	Plasmacytoid/signet ring cell/diffuse
Micropapillary	Sarcomatoid
Lymphoepithelioma-like	Giant cell
Lymphoma-like	Poorly differentiated
Plasmacytoid	Lipid rich
Sarcomatoid	Clear cell
Giant cell	Tumours of maüllerian type
Undifferentiated	Tumors arising in a bladder diverticulum

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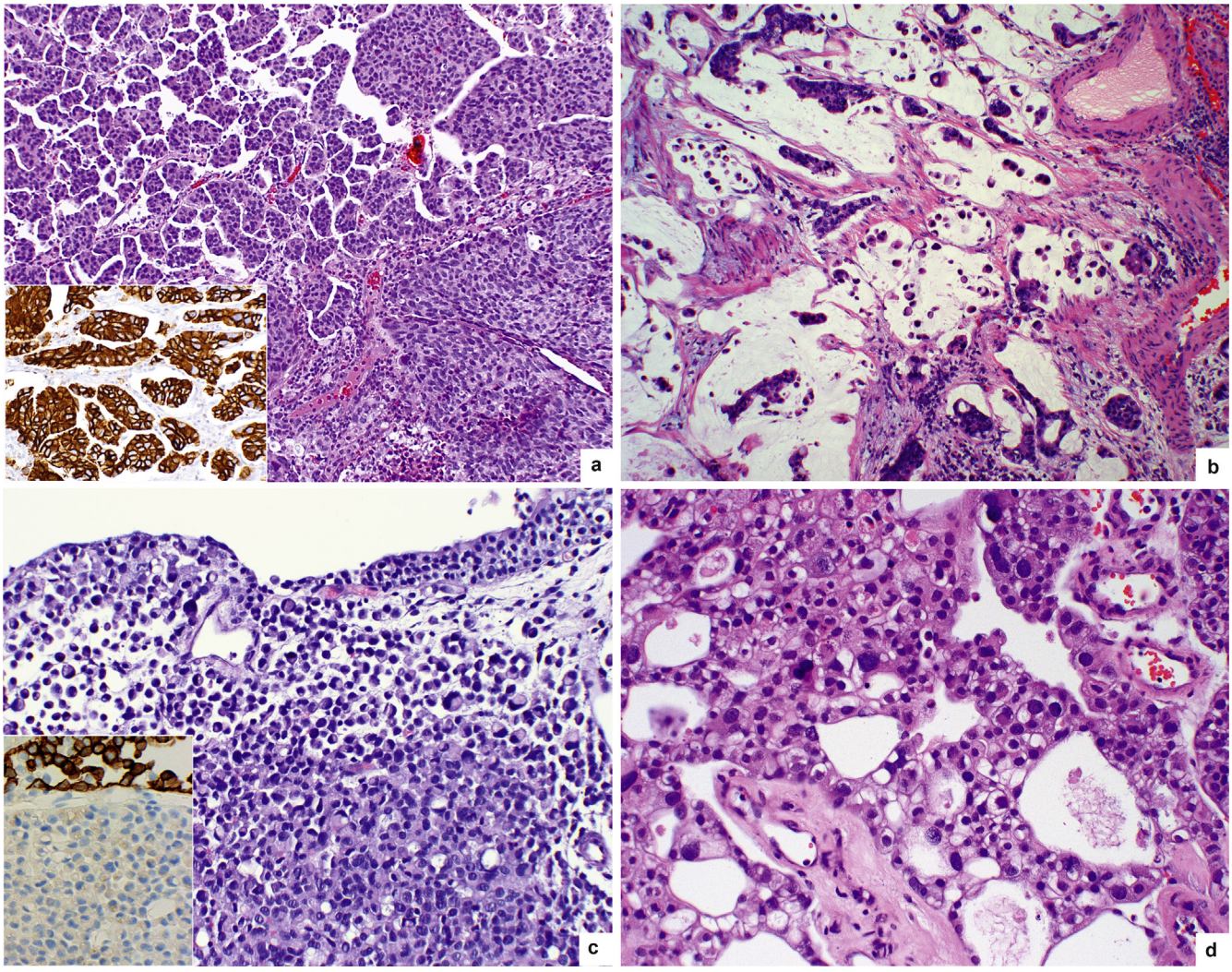

Fig. 5 – (a) Urothelial carcinoma with mixed histologic features (divergent differentiation), including a micropapillary component. Strong HER2 expression is preferentially seen in the micropapillary component (insert). (b) Adenocarcinoma of the bladder. This case has enteric features and extensive mucin production. Notice signet ring cells within the mucin. (c) Plasmacytoid carcinoma of the bladder. Notice the presence of both plasmacytoid and signet ring cells devoid of extracellular mucin. Insert demonstrates loss of e-cadherin expression within the invasive tumour, whereas it is retained in the surface urothelium. (d) Clear cell carcinoma. This tumour can arise from the surface urothelium or from müllerian rests located within or adjacent to the urogenital tract.

Common morphologic manifestations of divergent differentiation appear along squamous, glandular, small cell, and even trophoblastic lines. Squamous cell carcinoma is defined by the presence of intercellular bridges or keratinization and may be present in up to 40% of invasive urothelial carcinomas [63–66]. It is almost never associated with human papillomavirus infection, with the rare exception of some cases with a basaloid morphology [67,68]. Interestingly, recent genomic data have described a basal/squamous-like molecular subtype that has squamoid morphology and immunophenotype and is associated with poor survival and poor response to systemic therapy [69,70]. Glandular neoplasms constitute the second most common form of divergent differentiation, seen in up to 18% of invasive tumours and defined by the presence of gland formation [71–73]. These tumours commonly have enteric features and, in isolation, can be easily confused with colonic adenocarcinoma. These tumours can express an identical immunophenotype such that site of origin is best determined clinically. In this setting and in others in which the tumour is composed exclusively of a variant morphology, pathologists are encouraged to include a comment in the pathology report, stating, "We would accept as primary at this site if direct extension or a metastasis from another organ can be ruled out clinically." Some tumours are associated with extravasated mucin (mucinous), with or without signet ring cells [74]. Rare tumours exhibit trophoblastic differentiation (syncytiotrophoblasts) with human chorionic gonadotrophin production, and some may even have an endodermal sinus, which expresses α-fetoprotein [71,75].

Many other morphologic manifestations of divergent differentiation may be encountered including nested, micropapillary, and small cell. When present in a pure

form, these are considered variants of urothelial carcinoma. As mentioned previously, their presence in a tumour with mixed histology is of questionable clinical importance compared with urothelial carcinomas of equal stage and grade, although some exceptions exist, such as small cell carcinoma and possibly micropapillary carcinoma.

2.3. Invasive variants of urothelial carcinoma

The variants of urothelial carcinoma are listed in Table 1. This discussion will highlight only novel entities or novel concepts within selected variants.

The morphologic types of glandular neoplasms arising in the urothelial tract include enteric and mucinous types [71,74]. The enteric type is morphologically identical to its colonic counterpart, with which it can be easily confused. The mucinous type is characterized by the presence of abundant extravasated mucin with free-floating neoplastic cells, including signet ring cells (Fig. 5b). Contemporary thinking suggests that signet ring cell carcinoma, which by definition is not associated with any extravasated mucin, should not be included in this variant. Experience has taught us that tumours previously classified as such were either of the mucinous type or consisted of tumours with a variable number of signet ring cells as well as a significant number of cells with plasmacytoid features. In fact, plasmacytoid cells almost always predominate. These facts and recent molecular studies suggest that such tumours fit best in the *plamacytoid variant* category (described subsequently).

The nested variant of urothelial carcinoma is characterized by cytologically bland tumour cells, infiltrating as disorderly arranged, discrete or confluent small nests or tubules. A large nested variant of urothelial carcinoma has been described recently and is composed of equally bland tumour cells [76–79]. The importance of identifying this variant cannot be overstated because it can mimic benign urothelial proliferations, particularly in superficial transurethral resections and cold-cup biopsies, but it presents characteristically as locally advanced tumours and is associated with poor clinical outcome. The traditional grading scheme for urothelial carcinomas does not apply to these deceptively bland variants. Although the microcystic variant of urothelial carcinoma is considered a distinct entity, some examples can also have nests and tubules of neoplastic cells [80,81]. Importantly, what they also share is a deceptively bland cytologic appearance that can mimic benign conditions such as cystitis glandularis.

The micropapillary variant of urothelial carcinoma has been well documented in the literature [82–89]. Morphologically, it is defined as small nests and aggregates of tumour cells within lacunae. Multiple small nests without vascular cores are characteristic of this entity. The nuclei are markedly atypical and oriented to the periphery of the cell cluster. Cytoplasmic vacuoles with distortion of the nuclear contour are common. These tumours are commonly associated with lymphovascular invasion, present at a high pathologic stage, and exhibit aggressive clinical behaviour. Despite the early literature advocating early cystectomy in all cases, it remains controversial whether these tumours should be treated differently form other high-grade, locally advanced bladder tumours, particularly regarding early cystectomy or neoadjuvant therapy. Whether clinical outcome is related to the morphology per se or to the stage at presentation is unclear, as is whether the proportion of the micropapillary component influences outcome. At the molecular level, overexpression or amplification of *ERBB2* is more common in this variant than in conventional urothelial carcinoma (Fig. 5a) [89–91].

Plasmacytoid urothelial carcinoma was described several decades ago, but recent data have defined the morphologic spectrum, clinical behaviour, and genotype in a more comprehensive manner [92–98]. This rare tumour is characterized by the presence of mononuclear tumour cells with plasmacytoid, lymphoid, or even rhabdoid features. The tumour will very commonly exhibit a variable percentage of cells with cytoplasmic vacuoles, imparting the appearance of signet ring cells, with or without intracellular mucin but never associated with extracellular mucin (Fig. 5c). In fact, virtually every case of signet ring cell carcinoma of the urinary bladder that has been described in the literature would now be placed into this category of tumour, assuming absence of extracellular mucin. Of all the variants, this one is most likely to be encountered in its pure form, although it can also be seen in association with usual urothelial carcinoma or other variants. It is invariably diagnosed at a locally advanced stage and is associated with a dismal outcome. At the molecular level, these tumours are characterized by the presence of truncating mutations of *CDH1* and loss of e-cadherin expression (Fig. 5c) [97].

2.4. Tumours arising along the genitourinary tract but not of urothelial origin

As described previously, the morphologic plasticity seen in urothelial carcinoma is very broad and includes tumours with clear cell features [99–103]. However, a series of tumours is encountered predominantly in women and appears to arise from müllerian precursors present within the bladder wall or adjacent soft tissues, commonly endometriosis but rarely müllerianosis [99]. Clear cell carcinoma predominates, but occasional cases of endometrioid-type carcinoma have been described, only in women. Clear cell carcinomas are characterized by the usual tubulocystic, papillary, or diffuse growth patterns (Fig. 5d). Hobnail cells are common, as are basophilic or eosinophilic secretions. Although some cases may be confused with nephrogenic adenoma, the level of nuclear enlargement and hyperchromasia present in clear cell carcinoma should lead to the proper diagnosis. As might be expected, this tumour is immunoreactive for PAX8, HNF1B, CA125 and p53, similar to its ovarian counterparts. The endometrioid variant is usually PAX8 and p53 negative but positive for ER and PR.

2.5. Tumours arising in a bladder diverticulum

Epithelial neoplasms have been reported in up to 14% of bladder diverticula, composing approximately 1% of bladder neoplasms [104–106]. Based on the unique clinical

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scenario and anatomy of diverticula, it is an important topic that was not covered in the prior edition. The majority of tumours arise in acquired diverticula, the wall of which is composed of urothelium and lamina propria only; by definition, no muscularis propria is present except in the bladder wall immediately adjacent to the diverticulum (diverticular os). As such, pathologic staging of these tumours is different from those that arise within the bladder because pT2 disease does not exist. Up to 50% of cases are noninvasive, either papillary or flat. Of those tumours that are invasive, most are of usual urothelial type, whereas the rest may exhibit a variant morphology or mixed histologic features (divergent differentiation). Similar to vesical primaries, pathologic stage is the most important prognostic factor.

2.6. Genomics of urothelial carcinoma

Studies have suggested that invasive urothelial tumours develop along at least two molecular pathways, via either high-grade papillary tumours or CIS. Molecular alterations differ markedly between low- and high-grade tumours and between those that are invasive and those that are not. Because it is likely that tumours develop from areas of premalignant urothelial cells, it is not surprising that multifocal and metachronous tumours show common as well as novel uniquely acquired mutations [107–109]. Copy number abnormalities, loss of heterozygosity, and increased genomic instability have been associated with increasing tumour grade and stage. Multiple tumour suppressor genes and oncogenes have been described in invasive urothelial carcinoma, but often it is difficult to determine whether these are required for cancer development [110,111]. Recurrent mutations occur in genes such as *TP53, FGFR3, PIK3CA, RB1* and *HRAS*, with *TP53* and *FGFR3* being the most common, together with promoter mutations of *TERT* [112–114]. Although TERT mutations are present in up to 79% of bladder neoplasms, they have no association with clinical outcome; however, its presence can be of great diagnostic utility, given the relative rarity of this mutation in other tumours that may have overlapping histology. Next-generation sequencing efforts have demonstrated that the mutational landscape of urothelial tumours are quite complex, with >300 mutations, >200 copy number alterations, and >20 rearrangements per tumour [108,115–117]. Only lung cancer has been shown to harbour a higher rate of mutations, although most are certainly passenger mutations with no functional consequence [118].

The most frequently altered pathways in bladder cancer include the PI3K/AKT/mammalian target of rapamycin pathway [96,119–121], the FGFR3/RAF/RAS pathway, the *TP53/RB1* pathway, immune response checkpoint modulators [122,123], and chromatin-regulating and -remodelling genes [124–126]. In general, mutations along a given pathway are mutually exclusive. Some of the components of these pathways are altered in low-risk disease, whereas others are characteristic of high-risk disease. FGFR3 mutations, for example, are seen in up to 80% of papillary noninvasive and low-grade carcinomas. Although these mutations have been associated with a higher risk of recurrence, they are not associated with disease progression [11,127]. Mutations in chromatin-remodelling and histone-modifying genes have been described in up to 89% of muscularis propria invasive bladder tumours [116,128]. As novel therapeutic agents are developed that target these pathways, improvements in therapy will come. In addition, emerging data show that immune-modulating agents may have a promising role in the management of advanced urothelial carcinoma.

The discovery of the molecular pathways involved in urothelial cancer recurrence and progression has allowed for the identification of potential prognostic and predictive markers [116,129,130]. It has also permitted the development of novel noninvasive detection and surveillance strategies and revealed potential therapeutic targets [131–136]. The absence of multi-institutional randomized prospective trials, however, has delayed the validation of these prognostic and predictive markers for routine clinical use. The good news is that a significant number of these trials have been launched or will be in the near future and will likely alter the way we identify, risk-assess, and treat these tumours.

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Study concept and design: Humphrey, Moch, Cubilla, Ulbright, Reuter.
Acquisition of data: Humphrey, Moch, Cubilla, Ulbright, Reuter.
Analysis and interpretation of data: Humphrey, Moch, Cubilla, Ulbright, Reuter.
Drafting of the manuscript: Humphrey, Moch, Cubilla, Ulbright, Reuter.
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